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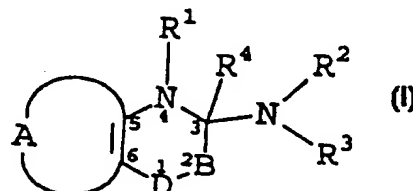
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(54) Title: PYRIDO-1,2,4-THIADIAZINE AND PYRIDO-1,4-THIAZINE DERIVATIVES, THEIR PREPARATION AND USE

(57) Abstract

Pyrido-1,2,4-thiadiazine and -1,4-thiazine derivatives represented by formula (I) wherein A, B, D, R¹, R², R³ and R⁴ are defined in the description, compositions thereof and methods for preparing the compounds are described. The compounds are useful in the treatment of diseases of the central nervous system, the cardiovascular system, pulmonary system, the gastrointestinal system and the endocrinological system.



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TITLE

Pyrido-1,2,4-Thiadiazine and Pyrido-1,4-Thiazine Derivatives, their Preparation and Use

FIELD OF THE INVENTION

The present invention relates to pyrido-1,2,4-thiadiazine and pyrido-1,4-thiazine derivatives, to methods for their preparation, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy e.g. in the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

BACKGROUND OF THE INVENTION

Potassium channels play an important role in membrane potential. Among the different types of potassium channels are the ATP-sensitive (K_{ATP}) channels which are regulated by changes in the intracellular concentration of adenosine triphosphate. The K_{ATP} -channels have been found in cells from various tissues such as cardiac cells, pancreatic-cells, skeletal muscles, smooth muscles, central neurons and adenohipophysis cells. The channels have been associated with diverse cellular functions for example hormone secretion (insulin from pancreatic beta-cells, growth hormone and prolactin from adenohipophysis cells), vasodilation (in smooth muscle cells), cardiac action potential duration, neurotransmitter release in the central nervous system.

Modulators of the K_{ATP} -channels have been found to be of importance for the treatment of various diseases. Certain sulfonylureas which have been used for the treatment of non-insulin-dependent diabetes mellitus act by stimulating insulin release through an inhibition of the K_{ATP} -channels on pancreatic beta-cells.

The potassium channel openers, which comprise a heterogeneous group of compounds, have been found to be able to relax vascular smooth muscles and have therefore been used for the treatment of hypertension.

In addition, potassium channel openers can be used as bronchodilators in the treatment of asthma and various other diseases.

Furthermore, potassium channel openers have been shown to promote hairgrowth, and have been used for the treatment of baldness.

Potassium channel openers are also able to relax urinary bladder smooth muscle and therefore, can be used for the treatment of urinary incontinence. Potassium channel openers which relax smooth muscle of the uterus can be used for treatment of premature labor.

By acting on potassium channels of the central nervous system these compounds can be used for treatment of various neurological and psychiatric diseases such as Alzheimer, epilepsy and cerebral ischemia.

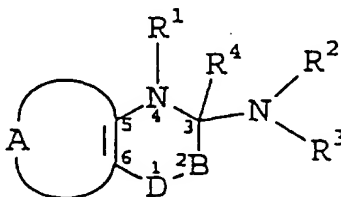
Recently, it has been shown that Diazoxide (7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide) and certain 3-(alkylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide derivatives inhibit insulin release by an activation of K_{ATP} -channels on pancreatic beta-cells (Pirrotte B. et al. *Biochem. Pharmacol.*, **47**, 1381-1386 (1994); Pirrotte B. et al., *J. Med. Chem.*, **36**, 3211-3213 (1993). Diazoxide has furthermore been shown to delay the onset of diabetes in BB-rats (Vlahos WD et al. *Metabolism* **40**, 39-46 (1991). In obese Zucker rats diazoxide has been shown to decrease insulin secretion and increase insulin receptor binding and consequently improve glucose tolerance and decrease weight gain (Alemzadeh R. et al. *Endocrinol.* **133**, 705-712, 1993). It is expected that such compounds can be used for treatment of diseases characterised by an overproduction of insulin and for the treatment and prevention of diabetes.

EP 618 209 discloses a class of pyridothiadiazine derivatives having an alkyl or an alkylamino group in position 3 of the thiadiazine ring. These compounds are claimed to be agonists at the AMPA-glutamate receptor.

In Acta Crystallographica Section C, 1995, C51(9), 1903-1905 the crystal structure of 3-benzamido-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide is described.

DESCRIPTION OF THE INVENTION

The present invention relates to pyrido-1,2,4-thiadiazine and pyrido-1,4-thiazine derivatives of the general formula I:



(I)

wherein

B represents $>NR^5$ or $>CR^5R^6$, wherein R^5 and R^6 independently can be hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen; or R^5 and R^6 together represent one of the bonds in a double bond between the atom 2 and 3 of formula I;

D represents $-S(=O)_2-$ or $-S(=O)-$; or

D-B represents $-S(=O)(R^{10})=N-$

wherein R^{10} is C_{1-6} -alkyl; or aryl or heteroaryl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6} -alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6} -monoalkyl- or dialkylamino, cyano, acyl, or C_{1-6} -alkoxycarbonyl;

R^1 is hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen and R^4 is hydrogen or R^4 together with R^5 represent one of the bonds in a double bond between the atoms 2 and 3 of formula I; or R^1 together with R^4 represent one of the bonds in a double bond between the atoms 3 and 4 of formula I;

R^2 is hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen;

R^3 is R^{11} ; $-OR^{11}$; $-C(=X)R^{11}$; $-NR^{11}R^{12}$; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6} -alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6} -monoalkyl- or dialkylamino, cyano, oxo, acyl or C_{1-6} -alkoxycarbonyl; or aryl substituted with C_{1-6} -alkyl;

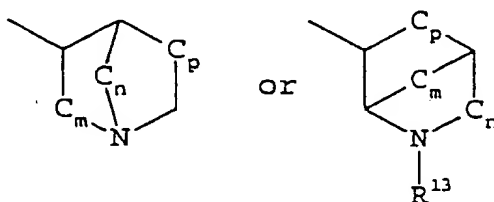
wherein R^{11} is hydrogen; C_{3-6} -cycloalkyl or $(C_{3-6}$ -cycloalkyl) C_{1-6} -alkyl, the C_{3-6} -cycloalkyl group optionally being mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms; or straight or branched C_{1-18} -alkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkylthio, C_{3-6} -cycloalkyl, aryl, aryloxy, arylalkoxy, nitro, amino, C_{1-6} -monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6} -alkoxycarbonyl, or carbamoyl;

X is O or S;

R^{12} is hydrogen; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{3-6} -cycloalkyl optionally mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy or

R^{11} and R^{12} together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, each of these ring systems optionally being mono- or polysubstituted with halogen, C_{1-6} -alkyl, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, nitro, amino, cyano, trifluoromethyl, C_{1-6} -monoalkyl- or dialkylamino, oxo; or

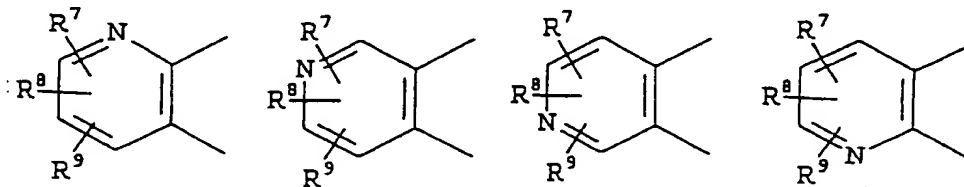
R^3 is



wherein n, m, p independently are 0, 1, 2, 3 and R^{13} is hydrogen; hydroxy; C_{1-6} -alkoxy; C_{3-6} -cycloalkyl optionally mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen;

or R^2 and R^3 together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, each of these ring systems optionally being mono- or polysubstituted with halogen, C_{1-6} -alkyl, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, nitro, amino, cyano, trifluoromethyl, C_{1-6} -monoalkyl- or dialkylamino or oxo;

A together with carbon atoms 5 and 6 of formula I forms a pyridine ring selected from



wherein R^7, R^8, R^9 independently are hydrogen; halogen; C_{1-12} -alkyl; C_{3-6} -cycloalkyl; hydroxy; C_{1-6} -alkoxy; C_{1-6} -alkoxy- C_{1-6} -alkyl; nitro; amino; cyano; cyanomethyl; perhalomethyl; C_{1-6} -monoalkyl- or dialkylamino; sulfamoyl; C_{1-6} -alkylthio; C_{1-6} -alkylsulfonyl; C_{1-6} -alkylsulfinyl; C_{1-6} -alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, the aryl group optionally being mono- or polysubstituted with C_{1-6} -

alkyl, halogen, hydroxy or C₁₋₆-alkoxy; C₁₋₆-alkoxycarbonyl; C₁₋₆-alkoxycarbonyl-C₁₋₆-alkyl; carbamyl; carbamylmethyl; C₁₋₆-monoalkyl- or dialkylaminocarbonyl; C₁₋₆-monoalkyl - or dialkylaminothiocarbonyl; ureido; C₁₋₆-monoalkyl- or dialkylaminocarbonylamino, thioureido; C₁₋₆-monoalkyl- or dialkylaminothiocarbonylamino; C₁₋₆-monoalkyl- or dialkylaminosulfonyl; carboxy; carboxy-C₁₋₆-alkyl; acyl; aryl, arylalkyl, aryloxy, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; (1,2,4-oxadiazol-5-yl)- or (1,2,4-oxadiazol-3-yl)-C₁₋₆-alkyl the oxadiazolyl group optionally being substituted with C₁₋₆-alkyl or C₃₋₆-cycloalkyl; or a 5 - 6 membered nitrogen containing ring, optionally substituted with phenyl or C₁₋₆-alkyl;

provided that when B represents NR⁵, D represents SO₂ and R² is hydrogen, C₁₋₆-alkyl or C₃₋₆-cycloalkyl, then R³ is not hydrogen, unsubstituted C₁₋₆-alkyl, C₃₋₆-cycloalkyl, (C₃₋₆-cycloalkyl)C₁₋₆-alkyl, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or benzoyl,

or a salt thereof with a pharmaceutically acceptable acid or base.

Within its scope the invention includes all optical isomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixture thereof.

The scope of the invention also includes all tautomeric forms of the compounds of formula I.

The salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethane sulfonic, picric and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference, or lithium, sodium, potassium, magnesium and the like.

The term "C₁₋₆-alkoxy" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C₁₋₆-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen and having 1 to 6 carbon atoms e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy.

The term "C₁₋₆-alkylthio" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a lower alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 6 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio.

The term "C₂₋₆-alkenyl" as used herein refers to an unsaturated hydrocarbon chain having 2-6 carbon atoms and one double bond such as e.g. vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl.

- 5 The term "C₃₋₆-cycloalkyl" as used herein refers to a radical of a saturated cyclic hydrocarbon with the indicated number of carbons such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "C₂₋₆-alkynyl" as used herein refers to unsaturated hydrocarbons which contain triple bonds, such as e.g. -C≡CH, -C≡CCH₃, -CH₂C≡CH, -CH₂CH₂C≡CH, -CH(CH₃)C≡CH, and the like.

10

The term "C₁₋₆-alkoxy-C₁₋₆-alkyl" as used herein refers to a group of 2-12 carbon atoms interrupted by an O such as e.g. CH₂-O-CH₃, CH₂-O-CH₂-CH₃, CH₂-O-CH(CH₃)₂ and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

15

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

20

The terms "C₁₋₆-alkyl", "C₁₋₁₂-alkyl" and "C₁₋₁₈-alkyl" as used herein, alone or in combination, refer to a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms such as e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylpentyl, neopentyl, n-hexyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl and the like. The term "C₁₋₁₈-alkyl" as used herein also includes secondary C₃₋₆-alkyl and tertiary C₄₋₆-alkyl.

25

The term "C₁₋₆-monoalkylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms such as e.g. methylamino, ethylamino, propylamino, n-butylamino, sec-butylamino, isobutylamino, tert-butylamino, n-pentylamino, 2-methylbutylamino, n-hexylamino, 4-methylpentylamino, neopentylamino, n-hexylamino, 2,2-dimethylpropylamino and the like.

30

The term "C₁₋₆-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino, and the like.

35

The term "acyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, and the like.

The term "C₁₋₆-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆ alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

The term "3-12 membered mono- or bicyclic system" as used herein refers to a monovalent substituent of formula -NR²R³ or -NR¹¹R¹² where R² and R³, or R¹¹ and R¹² together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, such as 1-pyrrolidyl, piperidino, morpholino, thiomorpholino, 4-methylpiperazin-1-yl, 7-azabicyclo[2.2.1]heptan-7-yl, tropanyl and the like.

The term "3-6 membered saturated ring system" as used herein refers to a monovalent substituent comprising a monocyclic saturated system containing one or more hetero atoms selected from nitrogen, oxygen and sulfur and having 3-6 members and having its free valence from a carbon atom, e.g. 2-pyrrolidyl, 4-piperidyl, 3-morpholinyl, 1,4-dioxan-2-yl, 5-oxazolidinyl, 4-isoxazolidinyl or 2-thiomorpholinyl.

The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl and 9-bicyclo[3.3.1]nonanyl.

The term "aryl" as used herein refers to phenyl, 1-naphthyl or 2-naphthyl.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

The term "arylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthyloxy or 2-naphthyloxy.

The term "arylalkoxy" as used herein refers to a C₁₋₆-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphthyl)ethoxy and the like.

5 The term "heteroarylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like.

10 The term "C₁₋₆-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl and 2,2-dimethylpropylsulfonyl.

15 The term "C₁₋₆-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a sulfonyl group such as e.g. methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl and 2,2-dimethylpropylaminosulfonyl.

20 The term "C₁₋₆-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-dialkylamino group linked through a sulfonyl group such as dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl, and the like.

30 The term "C₁₋₆-alkylsulfinyl" as used herein refers to a monovalent substituent comprising a straight or branched C₁₋₆-alkyl group linked through a sulfinyl group (-S(=O)-); such as e.g. methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, and the like.

35 The term "C₁₋₆-alkylcarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino, and the like.

The term "(C₃₋₆-cycloalkyl)C₁₋₆-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C₃₋₆-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl,

- halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl, and the like.

5 The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; e.g. phenylthio, (4-methylphenyl)-thio, (2-chlorophenyl)thio, and the like.

10 The term "arylsulfinyl" as used herein refers to an aryl group linked through a sulfinyl group (-S(=O)-), the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. phenylsulfinyl, (4-chlorophenyl)sulfinyl, and the like.

15 The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. phenylsulfonyl, tosyl, and the like.

20 The term "C₁₋₆-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylaminocarbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl.

25 The term "C₁₋₆-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-dialkylamino group linked through a carbonyl group such as dimethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl, and the like.

30 The term "C₁₋₆-monoalkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C₁₋₆-monoalkylaminocarbonyl group, e.g. methylaminocarbonylamino, ethylaminocarbonylamino, n-propylaminocarbonylamino, isopropylaminocarbonylamino, n-butylaminocarbonylamino, sec-butylaminocarbonylamino, isobutylaminocarbonylamino, tert-butylaminocarbonylamino, and 2-methylbutylaminocarbonylamino.

35

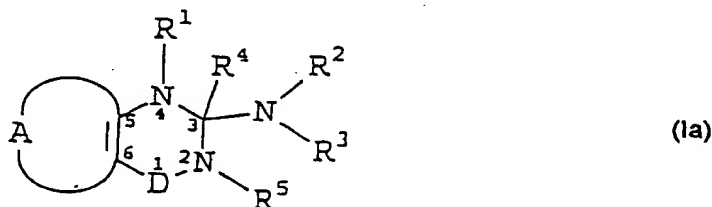
The term "C₁₋₆-dialkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C₁₋₆-dialkylaminocarbonyl group, such as dimethylaminocarbonylamino, N-ethyl-N-methylaminocarbonylamino, diethylaminocarbonylamino, dipro-

-pylaminocarbonylamino, N-(n-butyl)-N-methylaminocarbonylamino, di(n-pentyl)aminocarbonylamino, and the like.

The term "5- or 6-membered nitrogen containing ring" as used herein refers to a monovalent substituent comprising a monocyclic unsaturated or saturated system containing one or more nitrogen atoms and having 5 or 6 members, e.g. pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholino, thiomorpholino, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl and 1,4-dioxolanyl.

Within its scope the invention includes all optical isomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixture thereof.

In a preferred embodiment of the invention the general formula of formula I is selected from



wherein

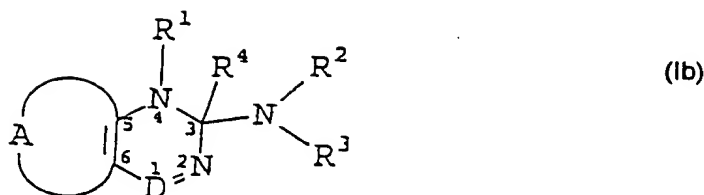
R¹ and R⁵ independently are hydrogen; hydroxy; C₁₋₆-alkoxy; or C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen and R⁴ is hydrogen; or

R⁴ together with R⁵ represent one of the bonds in a double bond between the atoms 2 and 3 of formula I and R¹ is as defined above; or

R⁴ together with R¹ represent one of the bonds in a double bond between the atoms 3 and 4 of formula I and R⁵ is as defined above;

D represents -S(=O)₂- or -S(=O)-.

In another preferred embodiment of the invention the general formula of formula I is selected from



5

wherein

R^1 is hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen and R^4 is hydrogen; or

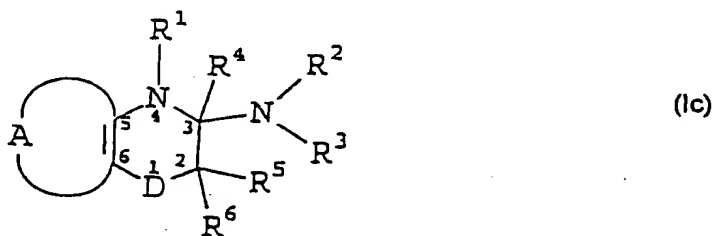
10 R^4 together with R^1 represent one of the bonds in a double bond between the atoms 3 and 4 of formula I;

D represents $-S(=O)R^{10}=$

15 wherein R^{10} is C_{1-6} -alkyl; aryl or heteroaryl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6} -alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6} -monoalkyl- or dialkylamino, cyano, acyl or C_{1-6} -alkoxycarbonyl.

In another preferred embodiment of the invention the general formula of formula I is selected from

20



25

wherein

R^1 , R^5 and R^6 independently are hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen and R^4 is hydrogen; or

30

R^4 together with R^5 represent one of the bonds in a double bond between the atoms 2 and 3 of formula I and R^1 and R^6 are as defined above; or

35 R^4 together with R^1 represent one of the bonds in a double bond between the atoms 3 and 4 of formula I and R^5 and R^6 are as defined above;

D represents $-S(=O)_2-$ or $S(=O)$.

Preferably, the general formula of formula I is (Ia).

5 In another preferred embodiment of the invention D is $-S(=O)_2-$.

In another preferred embodiment of the invention R^1 is selected from hydrogen, C_{1-6} -alkyl, C_{3-6} -cycloalkyl or C_{2-6} -alkenyl. Preferably R^1 is hydrogen or C_{1-6} -alkyl.

10 In another preferred embodiment of the invention R^1 together with R^4 represent one of the bonds in a double bond between the atoms 3 and 4 of formula I.

In another preferred embodiment of the invention R^4 together with R^5 represent one of the bonds in a double bond between the atoms 2 and 3 of formula I.

15

In another preferred embodiment of the invention R^2 is selected from hydrogen, hydroxy, C_{1-6} -alkyl, C_{3-6} -cycloalkyl or C_{2-6} -alkenyl.

In another preferred embodiment of the invention R^3 is selected from R^{11} ,
20 $-OR^{11}$, $-NR^{11}R^{12}$ or aryl, the aryl group optionally being substituted with C_{1-6} -alkyl; wherein R^{11} is hydrogen; C_{3-6} -cycloalkyl; $(C_{3-6}$ -cycloalkyl) C_{1-6} -alkyl; a 3-6 membered saturated ring system comprising one, two or three nitrogen-, oxygen- or sulfur atoms; or straight or branched C_{1-18} -alkyl optionally substituted with halogen, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkylthio, C_{3-6} -cycloalkyl or aryl; R^{12} is hydrogen, C_{1-6} -alkyl or C_{3-6} -cycloalkyl; or R^{11} and R^{12} together with the nitrogen atom form a 4 - 6
25 membered ring, preferably 1-pyrrolidyl, piperidine or morpholino.

In yet another preferred embodiment of the invention R^3 is selected from secondary C_{3-6} -alkyl, tertiary C_{4-6} -alkyl, C_{3-6} -cycloalkyl or $(C_{3-6}$ -cycloalkyl)methyl optionally mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy. Preferably R^3 is selected from isopropyl, 1-methylpropyl, 2-methylpropyl, tert-butyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1,2,2-trimethylpropyl, 2,3-dimethylbutyl, 1-ethylpropyl, 1-ethyl-2-methylpropyl, 1-ethyl-2,2-dimethylpropyl, 2,3,3-trimethylbutyl, 2-methylbutyl, cyclopropyl, 1-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, 1-(cyclopropyl)ethyl cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl.

35 In a further preferred embodiment of the invention R^2 and R^3 together with the nitrogen atom forms a six membered ring, optionally substituted in the 2-position with a C_{1-6} -alkyl group, preferably selected from methyl, ethyl or isopropyl. Preferably the six membered ring is a piperidine, piperazine, morpholine or thiomorpholine ring.

- In another preferred embodiment of the invention R^{10} is selected from C_{1-6} -alkyl, phenyl or pyridyl.

In another preferred embodiment of the invention R^7 , R^8 , R^9 are independently hydrogen; halogen; C_{1-12} -alkyl; C_{3-6} -cycloalkyl; cyano; cyanomethyl; perhalomethyl; sulfamoyl; C_{1-6} -alkylthio; C_{1-6} -alkylsulfonyl; C_{1-6} -alkylsulfinyl; arylthio, arylsulfinyl, arylsulfonyl, the aryl group optionally being mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; C_{1-6} -alkoxycarbonyl- C_{1-6} -alkyl; carbamylmethyl; carboxy- C_{1-6} -alkyl; aryloxy; (1,2,4-oxadiazol-5-yl)- or (1,2,4-oxadiazol-3-yl) C_{1-6} -alkyl, the oxadiazolyl group optionally being substituted with C_{1-6} -alkyl or C_{3-6} -cycloalkyl; acyl; or a 5 - 6 membered nitrogen containing ring, optionally substituted with phenyl or C_{1-6} -alkyl.

10

Preferred compounds of the invention are:

3-Hydrazino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;

15 3-Benzylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;

3-(R)-(1-Phenylethylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;

20

3-(S)-(1-Phenylethylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;

3-Benzylamino-7-chloro-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;

7-Chloro-3-(R)-(1-phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;

25 7-Chloro-3-(S)-(1'-phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;

3-Benzylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;

30

3-(R)-(1-Phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;

3-(S)-(1-Phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;

3-Hexylamino-4H- pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;

35 7-Chloro-3-hexylamino-4H- pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;

3-Octylamino-4H- pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;

- 7-Chloro-3-octylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Allylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 5 3-Allylamino-7-chloro-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 7-Chloro-3-(2-methoxy-1-methylethyl)amino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(2-Methoxy-1-methylethyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 10 3-(2-Hydroxy-1-methylethyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Benzylamino-2-methyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 15 2-Isopropylamino-3,3-dimethoxy-3H-pyrido[2,3-b][1,4]thiazine 4,4-dioxide.
- 3-Methoxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Ethoxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 20 3-Cyclopropylmethoxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Isopropoxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 25 3-Isobutoxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Butoxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 30 3-Cyclopentyloxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Allyloxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Benzylloxyamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 35 3-(2-Phenylethoxy)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(2-Methylhydrazino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;

- 3-(2-Ethylhydrazino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(2-Isopropylhydrazino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 5 3-(2-Methyl-2-ethylhydrazino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(2-Methyl-2-isopropylhydrazino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine
1,1-dioxide;
- 10 3-(2,2,2-Trifluoroethyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine
1,1-dioxide;
- 3-(1,1,1,3,3,3-Hexafluoro-2-propyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 15 3-(2-(1,1-Bis(trifluoromethyl)propyl))amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(1-Methyl-2,2,-difluoropropyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 20 3-(1-Methyl-2,2-dicyanoethyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine
1,1-dioxide;
- 3-(2-Bicyclo[2,2,2]octyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 25 3-(2-Adamantylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(1-Adamantylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(3-Quinuclidinyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 30 3-(1,5-dimethylhexyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(3-methylhexyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 35 3-(3-methylbutyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide.

The compounds of the present invention interact with the potassium channels and hence act as openers or blockers of the ATP-regulated potassium channels, which make them useful in the treatment of various diseases of the cardiovascular system, e.g. cerebral ischemia, hypertension,

ischemic heart diseases, angina pectoris and coronary heart diseases; the pulmonary system; the gastrointestinal system; the central nervous system and the endocrinological system.

Since some K_{ATP} -openers are able to antagonize vasospasms in basilar or cerebral arteries the compounds of the present invention can be used for the treatment of vasospastic disorders such as subarachnoid haemorrhage and migraine.

Potassium channel openers hyperpolarizes neurons and inhibit neurotransmitter release and it is expected that the present compounds can be used for the treatment of various diseases of the central nervous system, e.g. epilepsy, ischemia and neurodegenerative diseases, and for the management of pain.

By acting on potassium channels of the central nervous system the compounds of the present invention can be used for treatment of various neurological and psychiatric diseases such as Alzheimer, epilepsy and cerebral ischemia.

The compounds of the present invention may also be used for the treatment of diseases associated with decreased skeletal muscle blood flow such as Reynauds disease and intermittent claudication.

Further, the compounds of the invention may be used for the treatment of chronic airway diseases, including asthma, and for treatment of detrusor muscle instability secondary to bladder outflow obstruction and therefore for kidney stones by aiding their passage along the ureter. Potassium channel openers also relax urinary bladder smooth muscle, thus, the compounds of the present invention can be used for the treatment of urinary incontinence.

The present compounds could also be used for treatment of conditions associated with disturbances in gastrointestinal mobility such as irritable bowel syndrome. Additionally these compounds can be used for the treatment of premature labor and dysmenorrhea.

Further, potassium channel openers promote hairgrowth, therefore, the compounds of the present invention can be used for the treatment of baldness.

In diseases such as nesidioblastosis and insulinoma in which a hypersecretion of insulin causes severe hypoglycemia the compounds of the present invention can be used to reduce insulin secretion. In obesity hyperinsulinemia and insulin resistance is very frequently encountered. This condition could lead to the development of noninsulin dependent diabetes (NIDDM). It is expected that potassium channel openers and hence the compounds of the present invention can be used for contracting the hyperinsulinemia and thereby prevent diabetes and reduce obesity. In overt NIDDM treatment of

hyperinsulinemia with potassium channel openers, and hence the present compounds, can be of benefit in restoring glucose sensitivity and normal insulin secretions.

In early cases of insulin dependent diabetes (IDDM) or in prediabetic cases, potassium channel openers and hence the present compounds can be used to induce betacell rest which may prevent the progression of the autoimmune disease.

Compounds of the present invention which act as blockers of K_{ATP} -channels can be used for the treatment of NIDDM.

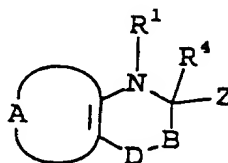
Preferably, the compounds of the present invention may be used for treatment or prevention of diseases of the endocrinological system such as hyperinsulinaemia and diabetes.

Accordingly, in another aspect the invention relates to a compound of the general formula I or a pharmaceutically acceptable acid addition salt thereof for use as a therapeutically acceptable substance, preferably for use as a therapeutically acceptable substance in the treatment of hyperinsulinaemia and treatment or prevention of diabetes.

Furthermore, the invention also relates to the use of the inventive compounds of formula I as medicaments useful for treating hyperinsulinaemia and treating or preventing diabetes.

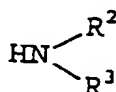
In yet another aspect, the present invention relates to methods of preparing the above mentioned compounds. The methods comprises:

a) reacting a compound of formula II:



(II)

wherein A, B, D, R^1 and R^4 are as defined above and Z is a leaving group such as imidazol-1-yl, alkoxy, alkylthio, halogen, preferentially chloro, bromo, iodo, trimethylamino, or methylsulfonyl with a compound of formula III:



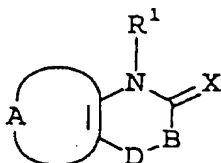
(III)

wherein R^2 and R^3 are defined above to form a compound of the general formula I using procedures described by e.g. T. H. Cronon et al., *J. Med. Chem.* 11, 136 (1968); L. Raffa et al., *Farmaco Ed. Sci.* 29, 411 (1974); B. Pirotte et al., *J. Med. Chem.* 36, 3211 (1993).

5 Another method comprises:

b) reacting a compound of formula IV:

10



(IV)

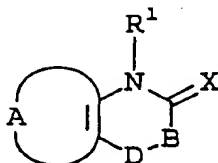
15

wherein R^1 is hydrogen and A, B, D and X are as defined above, or B is NH and R^1 , A, D and X are as defined above, with the compound of formula III, or a suitable salt thereof in the presence of P_2O_5 and a high boiling tertiary amine or a suitable salt thereof using a procedure described by Jensen K.G. and Pedersen E.B., *Chem. Scr.*, 20, 248-250 (1988) and Andersen L., Nielsen F.E. and Pedersen E.B., *Chem. Scr.*, 29, 45-49 (1989), to form a compound of the general formula I.

20

c) reacting a compound of the formula IV:

25



(IV)

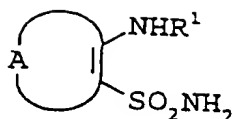
30

wherein R^1 is hydrogen and A, B, D and X are as defined above or B is NH and R^1 , A, D and X are as defined above, with a compound of the formula III, or a suitable salt thereof in the presence of titanium tetrachloride and a solvent with which it may form a complex, like e.g. tetrahydrofuran, or a mixture of toluene and anisole, according to the methods described in R.I. Fryer, J.V. Earley, G.F. Field, W. Zally, and L.H. Sternbach, *J. Org. Chem.* 34, 1143-1145 (1969); J.B. Press et al., *J. Med. Chem.* 22, 725-731 (1979); or G. Roma et al. *Eur. J. Med. Chem.* 26, 489-496 (1991), to form a compound of the general formula I.

35

d) reacting a compound of formula V

5



(V)

wherein R^1 and A are as defined above, with a compound of formula VI



(VI)

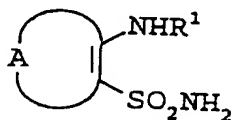
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wherein R^3 is as defined above using the method described by Chern J.W. et al., *J. Heterocycl. Chem.*, 27, 1909-1915 (1990), to form a compound of the general formula I, wherein D is SO_2 , B is $>NR^5$, R^2 is H, and R^4 and R^5 together form a bond.

15

e) reacting a compound of the formula V

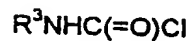
20



(V)

wherein R^1 and A are as defined above, with a compound of formula VII

25



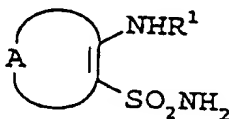
(VII)

wherein R^3 is as defined above using the method described by Chern J.W. et al., *J. Heterocycl. Chem.*, 27, 1909-1915 (1990), to form a compound of the general formula I, wherein D is SO_2 , B is $>NR^5$, R^2 is H, and R^4 and R^5 together form a bond.

30

f) reacting a compound of the formula V

35



(V)

wherein R¹ and A are defined as above, with a compound of formula VIII



wherein Y is NH or S, or a suitable salt thereof using procedures described by Kotovskaya S.K. et al., *Khim.-Farm. Zh.*, 13, 54-57 (russ.) (1979) and Topliss J.G. et al., *J. Org. Chem.*, 28, 2313 (1963), to form a compound of the general formula I, wherein D is SO₂, B is >NR⁵, R⁴ and R⁵ together form a bond, and R² and R³ are H.

The starting materials are either known compounds or compounds which may be prepared in analogy with the preparation of known compounds or in analogy with known methods as described by e.g. Huang B.-S., et al., *J. Med. Chem.*, 23, 575-7 (1980), Ofitserov V. I. et al., *Khim. Geterotsikl. Soedin.*, 1119-22 (russ.) (1976), Topliss J. G., U.S. 3,641,017 (1972), Kotovskaya S. K. et al., *Khim.-Farm. Zh.*, 13, 54-57 (russ.) (1979), Meyer R. F., *J. Heterocycl. Chem.*, 6, 407-408 (1969) and Hattori M., Yoneda M., and Goto M., *Bull. Chem. Soc. Jap.*, 46, 1890-1 (1973), Williams T.R. and Cram D.J., *J. Org. Chem.*, 38, 20-26 (1973), Barnes A.C., Kennewell P.D. and Taylor J.B., *J. Chem. Soc. Chem. Commun.*, 1973, 776-777, Stoss and Satzinger, *Chem. Ber.*, 109, 2097 (1976), Kresze G., Hatjiissaak A., *Phosphorus Sulfur*, 29, 41-47 (1987), Dillard R.D., Yen T.T., Stark P., Pavey D.E., *J. Med. Chem.*, 23, 717-722 (1980).

PHARMACOLOGICAL METHODS

The ability of the compounds to interact with potassium channels can be determined by various methods. When patch-clamp techniques (Hamill O.P., Marty A., Nefer E., Sakman B. and Sigworth F.J., *Plügers Arch.*, 391, 85-100 (1981)) are used the ionic current through a single channel of a cell can be recorded.

The activity of the compounds as potassium channel openers can also be measured as relaxation of rat aortas rings according to the following procedure:

A section of rat thoracic aorta between the aortic arch and the diaphragm was dissected out and mounted as ring preparations as described by Taylor P.D. et al., *Brit J. Pharmacol.*, 111, 42-48 (1994).

After a 45 min. equilibration period under a tension of 2 g, the preparations were contracted to achieve 80% of the maximum response using the required concentration of phenylephrine. When the phenylephrine response reached a plateau, potential vasodilatory agents were added cumulatively to the bath in small volumes using half log molar increments at 2 min intervals. Relaxation was

expressed at the percentage of the contracted tension. The potency of a compound was expressed as the concentration required to evoke a 50% relaxation of the tissue.

- 5 In the pancreatic β -cell the opening of the K_{ATP} -channels can be determined by measuring the subsequent change in the concentration of cytoplasmic free Ca^{2+} concentration according to the method of Arkhammer P. et al. , *J. Biol. Chem.*, 262, 5448-5454 (1987).

$^{86}Rb^{+}$ efflux from a β -cell line

- 10 The RIN 5F cell line was grown in RPMI 1640 with Glutamax I, supplemented with 10 % fetal calf serum (from GibcoBRL, Scotland, UK) and maintained in an atmosphere of 5 % CO_2 / 95 % air at 37°C. The cells were detached with a Trypsin-EDTA solution (from GibcoBRL, Scotland, UK), resuspended in medium, added 1 mCi/ml $^{86}Rb^{+}$ and replated into microtiter plates (96 well cluster 3596, sterile, from Costar Corporation, MA, USA) at a density of 50000 cells/well in 100 μ l/well, and
15 grown 24 hours before use in assay.

- The plates were washed 4 times with Ringer buffer (150 mM NaCl, 10 mM Hepes, 3.0 mM KCl, 1.0 mM $CaCl_2$, 20 mM Sucrose, pH 7.1). Eighty μ l Ringer buffer and 1 ml control- or test compound dissolved in DMSO was added. After incubation 1 h at room temperature with a lid, 50 μ l of the
20 supernatant was transferred to PicoPlates (Packard Instrument Company, CT, USA) and 100 μ l MicroScint40 (Packard Instrument Company, CT, USA) added. The plates were counted in TopCount (Packard Instrument Company, CT, USA) for 1 min/well at the ^{32}P program.

- The calculation of EC_{50} and E_{max} was done by SlideWrite (Advanced Graphics Software, Inc., CA, USA) using a four parameter logistic curve: $y = (a-d)/(1+(x/c)^b)+d$, where a = the activity estimated at
25 concentration zero, b = a slope factor, c = the concentration at the middle of the curve and, d = the activity estimated at infinite concentration. $EC_{50} = c$ and $E_{max} = d$, when the curve is turned of at infinite concentrations.

- 30 Measurement of insulin release from incubated pancreatic islets isolated by the collagenase method from fed female albino Wistar rats.

- Groups of 10 islets, each derived from the same batch of islets, are preincubated for 30 min at 37°C in 1 ml of a bicarbonate buffered solution (in mM : NaCl 115, KCl 5, $CaCl_2$ 2.56, $MgCl_2$ 1, $NaHCO_3$
35 24) supplemented with 2.8 mM glucose, 0.5% (w/v) dialysed albumin (fraction V, Sigma Chemical Co and equilibrated against a mixture of O_2 (95%) and CO_2 (5%). The groups of 10 islets are then incubated at 37°C for a further 90 min in 1 ml of the same bicarbonate buffered medium containing 16.7 mM glucose and, in addition, the selected test compounds.

In this procedure 6 to 8 series of 10 beakers are incubated simultaneously. For each serie, 8 beakers contain groups of 10 islets and 2 beakers are considered as control beakers (treated in the same manner, containing physiological medium but no islets). In order to ensure homogeneous distribution of islets among the different series, the collected islets are placed in succession in one beaker of each serie. The first and last series of 10 beakers (8 beakers with islets, 2 beakers without islets in each series) are incubated in the presence of 16.7 mM glucose (no added pharmacological compound; these series are regarded as control series). The 4-6 other series of 10 beakers are incubated in a 16.7 mM glucose medium enriched with the selected pharmacological compound (either different compounds or 1 or 2 compounds tested at different concentrations). After incubation, the incubation medium is removed from the beaker with a Pasteur pipette and stored at -20°C. The release of insulin is measured radioimmunologically using rat insulin as a standard. Experiments are repeated 2-4 times, on different days (which means on 2-4 different sources of pancreatic islets).

The islets-related variations (variations in the absolute values for insulin secretion from one to another immunoassay) led us to express the secretory rate with reference to a control value (100% = average of absolute values of the first and last series of beakers in each experiment : control series). Thus for each experimental series, the absolute values are expressed as % compared to the control condition within the same experiment.

At a concentration of 50 μ M several compounds potentially inhibit insulin release:

<u>Compound No.</u>	<u>% Residual insulin released</u>
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1	75
3	17.5
6	52.3

The compounds according to the invention are effective over a wide dosage range. In general satisfactory results are obtained with dosages from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, per day. A most preferable dosage is about 5 mg to about 200 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet, appropriate for use in this method, may be prepared by conventional tableting techniques and contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite®	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

Due to their high degree of activity, the compounds of the invention may be administered to an animal in need of such treatment, prevention, elimination, alleviation or amelioration of various diseases as mentioned above and especially of diseases of the endocrinological system such as hyperinsulinaemia and diabetes. Such animals include both domestic animals, e.g. household pets, and non-domestic animals such as wildlife. Preferably the animal is a mammal especially a human.

EXAMPLES

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The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples which, however, are not to be construed as limiting.

EXAMPLE 1

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Preparation of intermediates

3-Methylsulfonyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate

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(Compound I), was prepared according to the published procedure (B. Pirotte et al., J.Med.Chem.,1993, 36, 3211-3213.

7-Chloro-3-(imidazol-1-yl)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

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A solution of 2-amino-5-chloropyridine-3-sulfonamide (8.0 g) and thiocarbonyldiimidazole (20.5 g) in dioxane (80 mL) and DMF (20 mL) was refluxed for 3 h. The reaction was checked by t.l.c. When the reaction was complete, the solvents were removed under reduced pressure. The residue was dissolved in an aqueous solution of NaOH (4 g in 150 mL of water). The solution turns

30

rapidly to a suspension of the sodium salt of the title compound. The salt was collected by filtration and washed with a small volume of water. The salt was dissolved in hot water (200 mL), treated with charcoal, filtered and the filtrate was adjusted to pH 5-6 with 1N HCl. The precipitate was collected by filtration, washed with water and dried (yield: 8.8 g); m.p. 330-331 °C. (Compound II).

3-(Imidazol-1-yl)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

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The same procedure as described for Compound II was used starting from 2-aminopyridine-3-sulfonamide (5.0 g) and thiocarbonyldiimidazole (13 g) except that the sodium salt did not precipitate after the addition of NaOH. The alkaline solution was treated with charcoal, filtered and the

filtrate was adjusted to pH 5-6 with HCl 1N. The precipitate was collected by filtration, washed with water and dried (yield: 4.8 g); m.p. 312-314 °C. (Compound III).

5 2-Methyl-3-thioxo-2,3-dihydro-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

A solution of N-methyl-4-aminopyridine-3-sulfonamide (de Tullio et al., Tetrahedron 1995, 3221-3234) (5.0 g) and thiocarbonyldiimidazole (7.5 g) in dioxane (30 mL) and DMF (15 mL) was heated at 90 °C for 2 h. The solvents were removed by distillation under reduced pressure. The residue
10 was dispersed in 0.6N NaOH (20 mL) and stirred for 30 min. The alkaline solution was treated with charcoal, filtered, and the filtrate was adjusted to pH 4-5. The precipitate was collected by filtration, washed with water and dried (yield: 4 g); m.p. 195-198 °C. (Compound IV).

15 2-Methyl-3-methylsulfanyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

A solution of 2-methyl-3-thioxo-2,3-dihydro-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (1.0 g) in acetonitrile (20 mL) was supplemented with potassium carbonate (1.0 g), then with methyl iodide (1 mL). After 1 h at room temperature, the solvent was removed by distillation under reduced pressure. The residue was dispersed in water (50 mL) and the suspension was adjusted to pH 5
20 with formic acid. The insoluble material was collected by filtration, washed with water and dried (yield: 0.8 g); m.p. 135-138 °C. (Compound V).

25 1H-Pyrido[2,3-b][1,4]thiazin-2(3H)-thione

Thionation of 1H-pyrido[2,3-b][1,4]thiazin-2(3H)-one (prepared according to Dunn and Norrie, J.Prakt.Chem. 1990,332 (4) 444-452) with phosphorous pentasulfide in toluene by standard procedures (see e.g. H. Tawada et al., Chem.Pharm.Bull. 1990, 38, 1238-1245) gave the title compound; m.p. 233-234 °C. (Compound VI).

30 2-Isopropylamino-3H-pyrido[2,3-b][1,4]thiazine

1H-Pyrido[2,3-b][1,4]thiazin-2(3H)-thione (0.5 g) was dissolved in 10 ml of isopropylamine and allowed to stand for 45 min at room temperature. Then the excess of the amine was removed in vacuum and the solid residue was dissolved in 25 ml of ethyl acetate / methanol (4:1), treated with charcoal and filtered through a pad of silica. The filter was eluted with 2 X 10 ml of ethyl acetate / methanol (4:1). The filtrate was evaporated and the slowly crystallizing residue was triturated with 5 ml of ethyl acetate and then with 3 ml of diethyl ether. The crystals were filtered off and dried to give the
35 title compound; m.p. 135-139 °C. (Compound VII).

EXAMPLE 23-Hydrazino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

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3-Methylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate (1.0 g) was added to hydrazine hydrate (0.8 ml) and the mixture was heated to 70 °C for 30 min. After cooling, the reaction mixture was supplemented with methanol (10 ml) and the solvents were removed by distillation under reduced pressure. The residue was dissolved in NaOH 2M (20 ml), treated with charcoal, filtered, and
10 the filtrate was adjusted to pH 6-7 with HCl 1M. The precipitate so obtained was collected by filtration, washed with water and dried (yield: 0.8 g); m.p. 290-292 °C. (Compound 1).

EXAMPLE 315 3-Aralkylamino-4H-1,2,4-pyridothiadiazine 1,1-dioxides

A mixture of the appropriate precursor (Compound I, II, or III) (0.5 g) and the appropriate aralkylamine (2.5 mL) was refluxed for 30 min to 60 min (until completion of the reaction ; t.l.c.). After cooling, the reaction mixture was distributed between 0.5% aqueous NaOH (200 mL) and di-
20 ethylether (100 mL). The aqueous layer was separated and was treated with charcoal, then filtered. The filtrate was adjusted to pH 6-7 with formic acid. The resulting precipitate was collected by filtration, washed with water and dried (yield: 70-85 %).

In this way the following compounds were prepared:

25

3-Benzylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 198-201 °C. (Compound 2).

3-(R)-(1-Phenylethylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 236-238 °C.
(Compound 3).

30

3-(S)-(1-Phenylethylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 233-235 °C.
(Compound 4).

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3-Benzylamino-7-chloro-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 244-245 °C.
(Compound 5).

7-Chloro-3-(R)-(1-phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
m.p. 261-262 °C. (Compound 6).

- 7-Chloro-3-(S)-(1-phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 262-265 °C. (Compound 7).
- 5 3-Benzylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 232-233 °C. (Compound 8).
- 3-(R)-(1-Phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 207-210 °C. (Compound 9).
- 10 3-(S)-(1-Phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 213-214 °C. (Compound 10).

EXAMPLE 4

15 3-Hexylamino-4H- pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

3-Methylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate (0.5 g) and hexylamine (5.0 mL) were refluxed for 3-4 h (until completion of the reaction ; t.l.c.). The amine was distilled under reduced pressure. The residue was dissolved in 1N NaOH (150 mL), treated with charcoal, filtered, and the filtrate was adjusted to pH 5-6 with formic acid. The resulting precipitate was collected by filtration, washed with water and dried (yield: 0.38 g); m.p. 170-171 °C. (Compound 11).

In a similar manner the following compound was prepared:

25 7-Chloro-3-hexylamino-4H- pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 176-179 °C; from 7-chloro-3-(imidazol-1-yl)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide and hexylamine. (Compound 12).

30 EXAMPLE 5

3-Octylamino-4H- pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

35 A mixture of 3-methylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate (0.5 g), octylamine (0.5 mL) and m-chlorotoluene (3 mL) was refluxed for 2-3 h (until completion of the reaction ; t.l.c.). Most of the solvents were removed by distillation and the residue was dispersed in a mixture of water (30 mL) and methanol (30 mL) and supplemented with NaOH 10 % w/v in water (2 mL). The mixture was treated with charcoal, filtered, and the filtrate was adjusted to pH 6 with

1N HCl. The resulting precipitate was collected by filtration, washed with water and dried (yield: 0.29 g); m.p. 176-179 °C. (Compound 13).

In a similar manner the following compound was prepared:

5

7-Chloro-3-octylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 170-175 °C; from 7-chloro-3-(imidazol-1-yl)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide and octylamine. (Compound 14).

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EXAMPLE 6

3-Allylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

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A mixture of 3-methylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate (0.5 g) and allylamine (4 mL) was heated in a sealed bomb for 4-5 h at 120 °C. After cooling, the amine was removed by distillation under reduced pressure. The residue was dissolved in 0.5N NaOH, treated with charcoal, filtered, and the filtrate was adjusted to pH 6 with 1N HCl. The resulting precipitate was collected by filtration, washed with water and dried to give the title compound as a dihydrate (yield: 0.44 g); m.p. 206-208 °C. (Compound 15).

20

In a similar manner the following compound was prepared:

3-Allylamino-7-chloro-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide; m.p. 224-227 °C; from 7-chloro-3-(imidazol-1-yl)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide and allylamine. (Compound 16).

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EXAMPLE 7

7-Chloro-3-(2-methoxy-1-methylethyl)amino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

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A mixture of 7-chloro-3-(imidazol-1-yl)-4H-pyrido[2,3-e]-1,2,4-thiadiazine (0.5 g) and 2-amino-1-methoxypropane (5 mL) was refluxed for 24 h. The amine was removed by distillation under reduced pressure. The residue was dissolved in a small volume of 0.1N NaOH (20 mL), treated with charcoal, filtered and the filtrate was adjusted to pH 5-6. The suspension was conserved 24 h at +4 °C. The precipitate was collected by filtration, washed with the minimum of water and dried (yield: 0.25 g); m.p. 150-156 °C. (Compound 17).

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EXAMPLE 83-(2-Methoxy-1-methylethyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

5 The same procedure than above was used (except the starting material was 3-methylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate) up to the adjustment of the aqueous solution to pH 5-6. However, in this case, no precipitation occurred. Then, the solvent was removed by distillation under reduced pressure. The residue was dispersed in a small volume of water
10 (4 mL). The insoluble material was collected by filtration. The solid was dispersed in acetone (30 mL). The insoluble material was eliminated by filtration. The filtrate was concentrated under reduced pressure. The residue was solubilized in a small volume of acetone (3 mL). After a few minutes, a fine precipitate appears which was collected by filtration, washed with acetone and
15 dried to give the title compound as a monohydrate (yield: 0.1 g); m.p. 174-178 °C. (Compound 18).

EXAMPLE 93-(2-Hydroxy-1-methylethyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

20 A suspension of 3-methylsulfanyl-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide monohydrate and 2-amino-1-propanol (0.75 mL) was refluxed for 90 min (until completion of the reaction; t.l.c.). After cooling, the addition of diethylether (20 mL) gave rise to the separation of an oily residue. After decantation of the ethereal solution, the residue was solubilized in methanol (1 mL) and then
25 supplemented with diethylether (15 mL). An oily residue separated again. After decantation of the supernatant, the oily residue was solubilized in acetone (6 mL). A fine precipitate readily appeared. After 3 h at +4 °C, the resulting precipitate was collected by filtration, washed with acetone and dried (yield: 0.33 g); m.p. 213-216 °C. (Compound 19).

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EXAMPLE 103-Benzylamino-2-methyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

35 A solution of 2-methyl-3-methylsulfanyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (0.5 g) and benzylamine (0.5 mL) in dioxane (2.5 mL) was refluxed until completion of the reaction (t.l.c.). After cooling, the addition of ether gave rise to the precipitation of the title compound. The precipitate was collected by filtration, washed with ether and recrystallized from methanol-ether (yield: 0.4 g); m.p. 142-146 °C. (Compound 20).

EXAMPLE 112-Isopropylamino-3,3-dimethoxy-3H-pyrido[2,3-b][1,4]thiazine 4,4-dioxide

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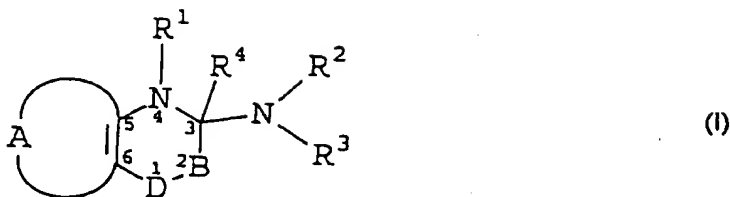
To a stirred solution of 2-isopropylamino-3H-pyrido[2,3-b][1,4]thiazine (0.10 g) in 2 ml of methanol was added 2 ml of water. To the resulting turbid mixture oxone (0.59 g) was added over 10 min and stirring was continued for 1 h. Then 10 ml of water was added and the mixture was extracted 3 times with 5 ml of dichloromethane. The combined extracts were dried over sodium sulfate and the solvent

10 was removed in vacuum. The residue was purified on a silica column eluted with a 9:1 mixture of ethyl acetate and methanol to give the title compound; m.p. 123-126 °C; m/e 299 (M+); ¹H-NMR(CDCl₃), δ (ppm): 7.92 (m, 1H, 6-H), 7.39-7.23 (m, 7-H and residual chloroform), 7.16-7.07 (m, 1H, 8-H), 5.79 (br d, 1H, NH), 4.2-4.0 (m, 1H, CH), 3.66 (s, 3H, CH₃O), 3.57 (s, 3H, CH₃O), 1.35-1.26 (two d, 6H, (CH₃)₂C). (Compound 21).

15

CLAIMS

1. A compound of the general formula I



wherein

B represents $>NR^5$ or $>CR^5R^6$, wherein R^5 and R^6 independently can be hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen; or R^5 and R^6 together represent one of the bonds in a double bond between the atom 2 and 3 of formula I;

D represents $-S(=O)_2-$ or $-S(=O)-$; or

D-B represents $-S(=O)(R^{10})=N-$

wherein R^{10} is C_{1-6} -alkyl; or aryl or heteroaryl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6} -alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6} -monoalkyl- or dialkylamino, cyano, acyl, or C_{1-6} -alkoxycarbonyl;

R^1 is hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen and R^4 is hydrogen or R^4 together with R^5 represent one of the bonds in a double bond between the atoms 2 and 3 of formula I; or R^1 together with R^4 represent one of the bonds in a double bond between the atoms 3 and 4 of formula I;

R^2 is hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen;

R^3 is R^{11} ; $-OR^{11}$; $-C(=X)R^{11}$; $-NR^{11}R^{12}$; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6} -alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6} -monoalkyl- or dialkylamino, cyano, oxo, acyl or C_{1-6} -alkoxycarbonyl; or aryl substituted with C_{1-6} -alkyl;

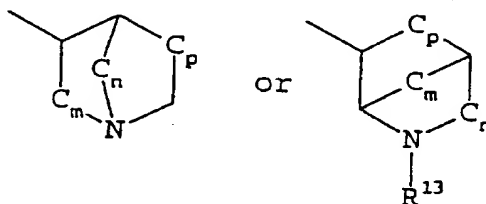
- wherein R^{11} is hydrogen; C_{3-6} -cycloalkyl or $(C_{3-6}$ -cycloalkyl) C_{1-6} -alkyl, the C_{3-6} -cycloalkyl group optionally being mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms; or straight or branched C_{1-6} -alkyl optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkylthio, C_{3-6} -cycloalkyl, aryl, aryloxy, arylalkoxy; nitro, amino, C_{1-6} -monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6} -alkoxycarbonyl, or carbamoyl;

X is O or S;

- R^{12} is hydrogen; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{3-6} -cycloalkyl optionally mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy or

- R^{11} and R^{12} together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, each of these ring systems optionally being mono- or polysubstituted with halogen, C_{1-6} -alkyl, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, nitro, amino, cyano, trifluoromethyl, C_{1-6} -monoalkyl- or dialkylamino, oxo; or

R^3 is



25

wherein n, m, p independently are 0, 1, 2, 3 and R^{13} is hydrogen; hydroxy; C_{1-6} -alkoxy; C_{3-6} -cycloalkyl optionally mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen;

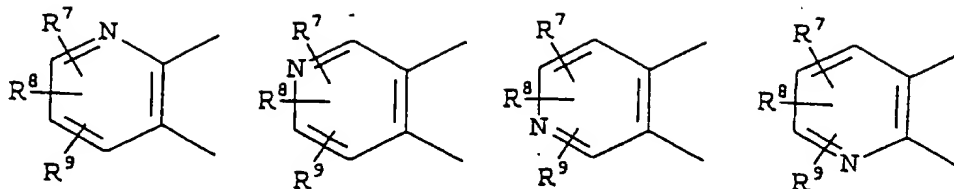
30

or R^2 and R^3 together with the nitrogen atom form a 3-12 membered mono- or bicyclic system, in which one or more of the carbon atoms may be exchanged with nitrogen, oxygen or sulfur, each of these ring systems optionally being mono- or polysubstituted with halogen, C_{1-6} -alkyl, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, nitro, amino, cyano, trifluoromethyl, C_{1-6} -monoalkyl- or dialkylamino or oxo;

35

A together with carbon atoms 5 and 6 of formula I forms a pyridine ring selected from

5



wherein R^7 , R^8 , R^9 independently are hydrogen; halogen; C_{1-12} -alkyl; C_{3-6} -cycloalkyl; hydroxy; C_{1-6} -alkoxy; C_{1-6} -alkoxy- C_{1-6} -alkyl; nitro; amino; cyano; cyanomethyl; perhalomethyl; C_{1-6} -monoalkyl- or dialkylamino; sulfamoyl; C_{1-6} -alkylthio; C_{1-6} -alkylsulfonyl; C_{1-6} -alkylsulfinyl; C_{1-6} -alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, the aryl group optionally being mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; C_{1-6} -alkoxycarbonyl; C_{1-6} -alkoxycarbonyl- C_{1-6} -alkyl; carbamyl; carbamylmethyl; C_{1-6} -monoalkyl- or dialkylaminocarbonyl; C_{1-6} -monoalkyl- or dialkylaminothiocarbonyl; ureido; C_{1-6} -monoalkyl- or dialkylaminocarbonylamino, thioureido; C_{1-6} -monoalkyl- or dialkylaminothiocarbonylamino; C_{1-6} -monoalkyl- or dialkylaminosulfonyl; carboxy; carboxy- C_{1-6} -alkyl; acyl; aryl, arylalkyl, aryloxy, the aryl group optionally being mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; (1,2,4-oxadiazol-5-yl)- or (1,2,4-oxadiazol-3-yl)- C_{1-6} -alkyl the oxadiazolyl group optionally being substituted with C_{1-6} -alkyl or C_{3-6} -cycloalkyl; or a 5 - 6 membered nitrogen containing ring, optionally substituted with phenyl or C_{1-6} -alkyl;

provided that when B represents NR^5 , D represents SO_2 and R^2 is hydrogen, C_{1-6} -alkyl or C_{3-6} -cycloalkyl, then R^3 is not hydrogen, unsubstituted C_{1-6} -alkyl, C_{3-6} -cycloalkyl, (C_{3-6} -cycloalkyl) C_{1-6} -alkyl, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or benzoyl.

2. A compound according to claim 1, wherein R^2 is hydrogen or C_{1-6} -alkyl.

25

3. A compound according to claim 1 or 2 wherein R^3 is R^{11} , $-OR^{11}$, $NR^{11}R^{12}$ or aryl, the aryl groups optionally being substituted with C_{1-6} -alkyl; wherein

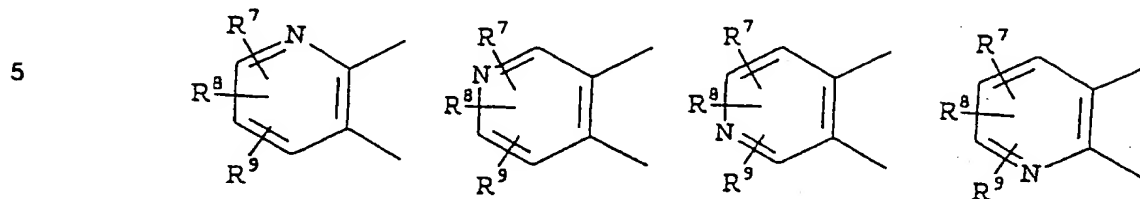
R^{11} is hydrogen; C_{3-6} -cycloalkyl; (C_{3-6} -cycloalkyl) C_{1-6} -alkyl; a 3 - 6 membered saturated ring system comprising one, two or three nitrogen-, oxygen- or sulfur atoms; or straight or branched C_{1-18} -alkyl optionally substituted with halogen, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkylthio, C_{3-6} -cycloalkyl or aryl,

R^{12} is hydrogen, C_{1-6} -alkyl or C_{3-6} -cycloalkyl; or

R^{11} and R^{12} together with the nitrogen atom form a 4 - 6 membered ring.

4. A compound according to any one of the preceding claims wherein R^3 is secondary C_{3-6} -alkyl, tertiary C_{4-6} -alkyl, C_{3-6} -cycloalkyl or (C_{3-6} -cycloalkyl)methyl.

5. A compound according to any one of the preceding claims wherein A together with carbon atoms 5 and 6 of formula I forms a pyridine ring selected from

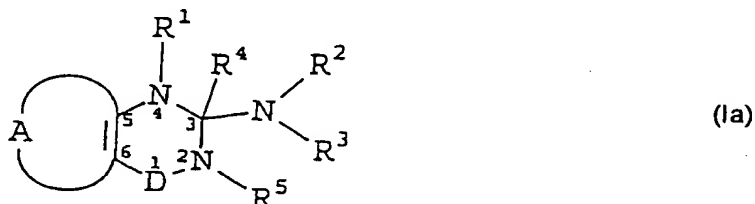


wherein

- 10 R^7 , R^8 , R^9 independently are hydrogen; halogen; C_{1-12} -alkyl; C_{3-6} -cycloalkyl; cyano; cyanomethyl; perhalomethyl; sulfamoyl; C_{1-6} -alkylthio; C_{1-6} -alkylsulfonyl; C_{1-6} -alkylsulfinyl; arylthio, arylsulfinyl, arylsulfonyl, the aryl group optionally being mono- or polysubstituted with C_{1-6} -alkyl, halogen, hydroxy or C_{1-6} -alkoxy; C_{1-6} -alkoxycarbonyl- C_{1-6} -alkyl; carbamylmethyl; carboxy- C_{1-6} -alkyl; aryloxy; (1,2,4-oxadiazol-5-yl)- or (1,2,4-oxadiazol-3-yl)- C_{1-6} -alkyl, the oxadiazolyl group optionally being substituted
- 15 with C_{1-6} -alkyl or C_{3-6} -cycloalkyl; acyl or a 5 - 6 membered nitrogen containing ring, optionally substituted with phenyl or C_{1-6} -alkyl.

6. A compound according to any one of the claims 1 - 5, wherein the general formula I is

20



25

wherein

- R^1 and R^5 independently are hydrogen; hydroxy; C_{1-6} -alkoxy; or C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl optionally mono- or polysubstituted with halogen and R^4 is hydrogen; or

30

R^4 together with R^5 represent one of the bonds in a double bond between the atoms 2 and 3 of formula I and R^1 is as defined above; or

35

R^4 together with R^1 represent one of the bonds in a double bond between the atoms 3 and 4 of formula I and R^5 is as defined above;

D represents $-S(=O)_2-$ or $S(=O)-$; and

- A, R² and R³ are as defined above.

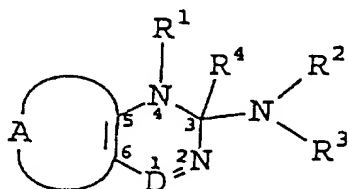
7. A compound according to claim 6 wherein R¹ and R⁵ independently are hydrogen or C₁₋₆-alkyl.

8. A compound according to claims 6 or 7 wherein R¹ together with R⁴ represent one of the bonds in a double bond between the atoms 3 and 4 of formula I.

9. A compound according to any one of the claims 6 - 8, wherein R⁴ together with R⁵ represent one of the bonds in a double bond between the atoms 2 and 3 of formula I.

10. A compound according to any one of the claims 6 - 9 wherein D is -S(=O)₂-.

11. A compound according to any one of the claims 1 - 5 wherein the general formula I is



(Ib)

wherein

R¹ is hydrogen; hydroxy; C₁₋₆-alkoxy; or C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen and R⁴ is hydrogen; or

R⁴ together with R¹ represent one of the bonds in a double bond between the atoms 3 and 4 of formula I;

D represents -S(=O)R¹⁰=

wherein R¹⁰ is C₁₋₆-alkyl; or aryl or heteroaryl optionally mono- or polysubstituted with halogen, hydroxy, C₁₋₆-alkoxy, aryloxy, arylalkoxy, nitro, amino, C₁₋₆-monoalkyl- or dialkylamino, cyano, acyl or C₁₋₆-alkoxycarbonyl; and

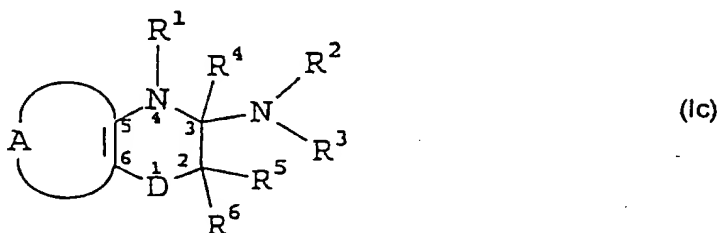
A, R² and R³ are as defined above.

12. A compound according to claim 11 wherein R¹ is hydrogen or C₁₋₆-alkyl.

13. A compound according to claim 11 or 12 wherein R¹ together with R⁴ represent one of the bonds in a double bond between the atoms 3 and 4 of formula I.

14. A compound according to any one of the claims 11 - 13 wherein R¹⁰ is C₁₋₆-alkyl, phenyl or pyridyl.

15. A compound according to any one of the claims 1 - 5 wherein the general formula I is



15. wherein

R¹, R⁵ and R⁶ independently are hydrogen; hydroxy; C₁₋₆-alkoxy; or C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl optionally mono- or polysubstituted with halogen and R⁴ is hydrogen; or

20 R⁴ together with R⁵ represent one of the bonds in a double bond between the atoms 2 and 3 of formula I and R¹ and R⁶ are as defined above; or

R⁴ together with R¹ represent one of the bonds in a double bond between the atoms 3 and 4 of formula I and R⁵ and R⁶ are as defined above;

25 D represents -S(=O)₂- or -S(=O)-; and

A, R², R³ are as defined above.

30 16. A compound according to claim 15 wherein R¹, R⁵ and R⁶ independently are hydrogen or C₁₋₆-alkyl.

17. A compound according claim 15 or 16 wherein R¹ together with R⁴ represent one of the bonds in a double bond between the atoms 3 and 4 of formula I.

35 18. A compound according to any one of the claims 15 - 17 wherein R⁴ together with R⁵ represent one of the bonds in a double bond between the atoms 2 and 3 of formula I.

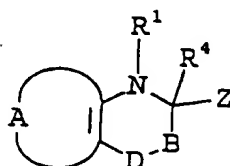
19. A compound according to any one of the claims 15 - 18 wherein D is -S(=O)₂-.

20. A compound selected from the following:

- 3-Hydrazino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Benzylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 5 3-(R)-(1-Phenylethylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(S)-(1-Phenylethylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Benzylamino-7-chloro-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 7-Chloro-3-(R)-(1-phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 7-Chloro-3-(S)-(1'-phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 10 3-Benzylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(R)-(1-Phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(S)-(1-Phenylethylamino)-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(Hexylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 7-Chloro-3-hexylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 15 3-Octylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 7-Chloro-3-octylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Allylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Allylamino-7-chloro-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 7-Chloro-3-(2-methoxy-1-methylethyl)amino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 20 3-(2-Methoxy-1-methylethyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-(2-Hydroxy-1-methylethyl)amino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 3-Benzylamino-2-methyl-2H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide;
- 2-Isopropylamino-3,3-dimethoxy-3H-pyrido[2,3-b][1,4]thiazine 4,4-dioxide.

25 21. Compounds according to any one of the preceding claims which acts as openers of the K_{ATP} -regulated potassium channels.

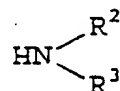
22. A method of preparing a compound of formula I, characterized in
a) reacting a compound of formula II:



(II)

wherein A, B, D, R¹ and R⁴ are as defined above and Z is a leaving group such as imidazol-1-yl, alkoxy, alkylthio, halogen, preferentially chloro, bromo, iodo, trimethylamino, or methylsulfonyl with a compound of formula III:

5

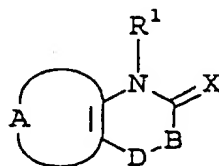


(III)

10 wherein R² and R³ are defined above to form a compound of the general formula I;

b) reacting a compound of formula IV:

15

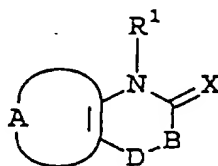


(IV)

20 wherein R¹ is hydrogen and A, B, D and X are as defined above, or B is NH and R¹, A, D and X are as defined above, with the compound of formula III, or a suitable salt thereof in the presence of P₂O₅ and a high boiling tertiary amine or a suitable salt thereof, to form a compound of the general formula I;

25 c) reacting a compound of the formula IV:

30



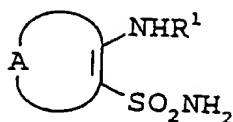
(IV)

35

wherein R¹ is hydrogen and A, B, D and X are as defined above or B is NH and R¹, A, D and X are as defined above, with a compound of the formula III, or a suitable salt thereof in the presence of titanium tetrachloride and a solvent with which it may form a complex, like e.g. tetrahydrofuran, or a mixture of toluene and anisole, to form a compound of the general formula I;

d) reacting a compound of formula V

5



10

(V)

wherein R^1 and A are as defined above, with a compound of formula VI



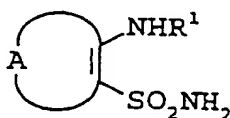
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(VI)

wherein R^3 is as defined above, to form a compound of the general formula I, wherein D is SO_2 , B is $>NR^5$, R^2 is H, and R^4 and R^5 together form a bond;

20 e) reacting a compound of the formula V

25



(V)

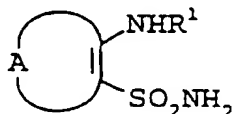
wherein R^1 and A are as defined above, with a compound of formula VII



(VII)

wherein R^3 is as defined, to form a compound of the general formula I, wherein D is SO_2 , B is $>NR^5$, R^2 is H, and R^4 and R^5 together form a bond; or

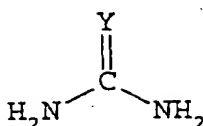
35 f) reacting a compound of the formula V



(V)

wherein R¹ and A are defined as above, with a compound of formula VIII

5



(VIII)

10 wherein Y is NH or S, or a suitable salt thereof, to form a compound of the general formula I, wherein D is SO₂, B is >NR⁵, R⁴ and R⁵ together form a bond, and R² and R³ are H.

23. A pharmaceutical composition comprising a compound according to any of the claims 1 - 21
or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any
15 optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form
together with one or more pharmaceutically acceptable carriers or diluents.

24. A pharmaceutical composition for use in the treatment of diseases of the endocrinological
system such as hyperinsulinaemia and diabetes comprising a compound according to any of the
20 claims 1 - 21 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or
base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any
tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

25. The pharmaceutical composition according to claim 23 or 24 in the form of an oral dosage
25 unit or parenteral dosage unit.

26. A pharmaceutical composition according to claim 23 or 24 wherein said compound is
administered as a dose in a range from about 0.05 to 1000, preferably from about 0.1 to 500 and
especially in the range from 5 to 200 mg per day.

30

27. A compound according to any of the claims 1 - 21 or a pharmaceutically acceptable salt
thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical
isomers, including a racemic mixture, or any tautomeric form for therapeutical use.

35 28. A compound according to any of the claims 1 - 21 or a pharmaceutically acceptable salt
thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical
isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or
prevention of diseases of the endocrinological system, such as hyperinsulinaemia and diabetes.

29. The use of a compound according to any of the claims 1 - 21 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form as a medicament.
- 5 30. The use of a compound according to any of the claims 1 - 21 for preparing a medicament.
31. The use of a compound according to any of the claims 1 - 21 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of
10 a medicament for the treatment or prevention of diseases of the endocrinological system, such as hyperinsulinaemia and diabetes.
32. A method of treating or preventing diseases of the endocrinological system, such as hyperinsulinaemia and diabetes in a subject in need thereof comprising administering an effective
15 amount of a compound according to any of the claims 1 - 21 to said subject.
33. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of diseases of the endocrinological system, such as hyperinsulinaemia and diabetes which process comprising bringing a compound of formula I according to any of the claims 1 - 21 or a
20 pharmaceutically acceptable salt thereof into a galenic dosage form.
34. Any novel feature or combination of features as described herein.

INTERNATIONAL SEARCH REPORT

International application No. ...
PCT/DK 97/00018

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: C07D 513/04, C07D 487/04, A61K 31/54 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: C07D, A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CA, WPI		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0618209 A1 (ADIR ET COMPAGNIE), 5 October 1994 (05.10.94) --	1-28,30,31, 33,34
X	Biochemical Pharmacology, Volume 47, No 8, 1994, B. Pirotte et al, "A Pyridothiadiazine (BPDZ 44) as a new and potent activator of ATP-Sensitive K+Channels" page 1381 - page 1386 --	1-28,30,31, 33,34
X	J. Med. Chem., Volume 36, 1993, Bernard Pirotte et al, "3-(Alkylamino)-4H-pyrido(4,3-e)-1,2, 4-thiadiazine 1,1-Dioxides as Powerful Inhibitors of Insulin Release from Rat Pancreatic B-Cells: A New Class of Potassium Channel Openers?" page 3211 - page 3213 --	1-28,30,31, 33,34
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
14 April 1997		26 -04- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00018

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1368948 A (MANUFACTURE DE PRODUITS PHARMACEUTIQUES A. CHRISTIAENS S.A.), 2 October 1974 (02.10.74) --	1-28, 33, 34
X	Acta Cryst., Volume C51, 1995, Léon Dupont, "3-Benzamido-4H-pyrido(4,3-e)-1,2,4-thiadiazine 1, 1-Dioxide" page 1903 - page 1905 --	1-28, 33, 34
X	Metabolism, Volume 40, No 8, August 1991, William D. Vlahos et al, "Diabetes Prevention in BB Rats by Inhibition of Endogenous Insulin Secretion" page 825 - page 829 -- -----	1-28, 30, 31, 33, 34

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00018

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 29, 32
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

04/03/97

International application No.
PCT/DK 97/00018

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0618209 A1	05/10/94	AU 673893 B	28/11/96
		AU 5904894 A	29/09/94
		CA 2119853 A	27/09/94
		FR 2703051 A,B	30/09/94
		JP 2513989 B	10/07/96
		JP 7002872 A	06/01/95
		NZ 260186 A	26/07/95
		US 5459138 A	17/10/95
		ZA 9402131 A	05/04/95
GB 1368948 A	02/10/74	AT 321301 B	25/03/75
		AT 324341 B	25/08/75
		BE 775166 A	10/05/72
		CA 1008859 A	19/04/77
		DE 2155483 A	08/06/72
		FR 2113927 A,B	30/06/72
		LU 64237 A	29/05/72
		NL 7115510 A	15/05/72
		US 3819639 A	25/06/74
		US 3980652 A	14/09/76
		US 3991057 A	09/11/76
		US 4002629 A	11/01/77

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